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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,350	09/05/2003	Robert C. Ladner	10280-053001	8718

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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,350	LADNER ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see office action*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election of Invention & Status of Claims

Applicant's election with traverse of Group I in the reply filed on July 25, 2006, is acknowledged. The traversal is on the grounds that it would not be an undue burden to search both the invention of Group I and Group II at the same time. Applicants appear to be of the opinion that the additional search of the first and second targets of Group II, as well as the arrangement between the target/cell, phage, and bead of Group II, in comparison to Group I, would not unduly burden the office. Applicants' arguments have been fully considered, and are not found persuasive.

As explained in the Restriction Requirement, art which discloses the enrichment of a phage library against a single target by repeated screening (such as in claim 1, where the exact same chemical target is used), is not necessarily related to art that first screens a phage library against a first target, followed by a screen of certain selected phage in the library against a completely unique and different chemical entity (*i.e.*, the second target, as in claim 19). For example, Al-bukhari is related to screening a phage library against a single target (see section 2.3 on page 165), similar to claim 1, but not to two different targets as in claim 19. According, the restriction requirement is proper, and is made final.

Pending claims 1-18 and 20-28 will be examined on the merits; pending claim 19 is withdrawn as being directed to a non-elected invention.

Objection to the Abstract Under 37 C.F.R. § 1.72

The abstract of the disclosure is objected to because it does not allow the public generally to determine quickly from a cursory inspection the nature and gist of the invention. Applicants should amend the abstract so that it corresponds to at least one independent claim. For example, Applicants should describe/surmise the series of method steps a) . *See* 37 C.F.R. § 1.72. Should Applicants amend the claims in their next reply, the amended abstract should take into account any further limitations added to the broadest independent claim.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on January 30, 2006, has been considered by the Examiner. The submission is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and all claims dependent therefrom, are indefinite for reciting the phrase "in the presence of the target thereby forming replicate phage-immobilized target complexes," because it appears that the product of forming replicate phage in the presence of a target forms a phage-target complex, not a phage-immobilized target complex. Applicants have not made it clear that the target in this step has been immobilized. Correction is required.

Claim 1, and all claims dependent therefrom, are indefinite for reciting the term "diverse" because one or ordinary skill in the art cannot reasonably determine which library member would be considered diverse and those that are not. The term is not used as an art-accepted term with a definite meaning, and is not defined in the specification. Correction is required.

Claims 15 and 16 are indefinite for reciting the phrase "producing e)" because it appears that claim text has been omitted and the claim is unclear. Correction is required.

Claim 20, and all claims dependent therefrom, recite the limitation "each input phage" in step (d)(1). There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7, 9-15, 20-24 and 26-28, are rejected under 35 U.S.C. § 102(a) as being anticipated by Al-bukhari *et al.*, *Journal of Immunological Methods 264*:163-171 (**2002**).

Claim 1 is directed to selecting phage that encode a target binding protein from a plurality of display phage, the method comprising: a) forming a mixture comprising a plurality of diverse display phage, a target, and a support, wherein each phage of the plurality displays a heterologous protein component on its surface and each phage includes a nucleic acid encoding the heterologous protein component, the heterologous protein component being a member of a set of diverse protein components; b) forming phage-immobilized target complexes, each of which comprises a phage from the plurality which binds the target and the target immobilized to the support; c) separating phage that do not bind to the target from the phage-immobilized target complexes; d) contacting host cells with the phage-immobilized target complexes so that the host cells are infected by phage from the phage-immobilized target complexes to yield a first population of infected cells; e) producing replicate phage from the infected cells in the presence of the target thereby forming replicate phage-immobilized target complexes; f) separating replicate phage that do not bind to the target from the replicate phage-immobilized target complexes; and g) contacting host cells with the replicate phage-immobilized target complexes so that host cells are infected with the replicate phage to yield a second population of infected cells.

Al-bukhari teaches the method of claim 1:

> "GAD-6 mAb (10 Ag/ml), or 10 µl of N-mAb or CmAb in 1 ml 0.05 M sodium carbonate/sodium bicarbonate buffer pH 9.6, was coated onto Nunc immuno-tubes that were subsequently blocked with 5% bovine serum albumin (BSA) in Tris-buffered saline (TBS).
>
> The constrained 9-mer T7 phage random peptide display library [about $1x10^{10}$ plaque forming units (pfu) per tube] was added to antibody-coated

> tubes and incubated at 4 °C for 20–30 min. The tubes were washed extensively in TBS–0.1% Tween-20 (TBS–T) and then 1 ml of a mid-log phase *E. coli* BL 21 culture was added and incubated at room temperature for 5 min for infection by the bound phage (termed the 'eluate'). The eluate phage were amplified and subjected to three further rounds of selection, as above."

Al-bukhari, page 165, col. 1, in section 2.3. Al-bukhari also describes the T7 phage library:

> "A T7 phage library was constructed that was designed to express 9-mer peptides that were constrained by a disulphide bridge between cysteine residues immediately adjacent to both ends of the 9-mer. The peptides were expressed near the C-terminus of the T7 gene X surface coat protein (415 copies per phage). The random peptides of the T7 library were encoded by double stranded DNA inserts assembled from synthetic degenerate oligonucleotides and cloned into gene X of the vector (T7select415-1) (Bioscience, Cambridge, UK) at *HindIII* and *EcoRI* restriction sites. The vector DNA and insert DNA were ligated with T4 DNA ligase, and assembled into phage using T7Select packaging extract (BioScience, Cambridge, UK). The phage were amplified in *E. coli* BL21."

Al-bukhari, beginning on page 164, col. 2, section 2.2, through page 165 of section 2.2.

Accordingly, claim 1 is anticipated. Claims 20 and 24 have the additional limitation that the nucleic acid of the phage is recovered; Al-bukhari teaches recovering the nucleic acid encoding the heterologous protein (page 165, col. 2, second full paragraph).

As in claims 2 and 3, Al-bukhari recovers a second round of cells and phage (Al-bukhari, section 2.3). As in claim 4, the steps are repeated; Al-bukhari teaches four rounds of selection (Al-bukhari, section 2.3). As in claims 5 and 6, the steps are repeated in the same vessel (Al-bukhari, section 2.3). As in claim 7, Al-bukhari does not add any additional target (Al-bukhari, section 2.3). As in claims 9 and 11, fewer that 5000 phage per cell are produced and the cell divides less than seven times. As in claims 10 and 12, Al-bukhari teaches the steps in less than 4 hours (see paragraph 2 in section 2.3 of Al-bukhari on page 165). As in claims 13 and 14, Al-bukhari teaches a diverse phage library, and a change in temperature, respectively (see paragraph 2 in section 2.3 of Al-bukhari on page 165). As in claim 15, the T7 phage has genes sufficient for phage replication in the host cell (section 2.2).

As in claim 21, Al-bukhari teaches amplifying in the presence of the target, *i.e.*, in the tubes. As in claim 22, the target is immobilized. As in claim 23, Al-bukhari teaches the binding and immobilizing (same sections of Al-bukhari as cited above).

Claims 26 and 27 are directed to the method of claim 24, wherein at least two and three cycles are performed respectively; Al-bukhari teaches four cycles (see captioned section above). As in claim 28, Al-bukhari completes each cycle in less than eight hours).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-7, 9-15 and 20-28, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Al-bukhari *et al.*, *Journal of Immunological Methods 264*:163-171 (**2002**), in view of Srivastava, U.S. Patent No. 6,797,480 B1.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The limitations of claims 1-7, 9-15, 20-24 and 26-28, and the corresponding disclosure of Al-bukhari is cited above and herein incorporated by reference.

Claim 25 is directed to varying the stringency in the during the separation cycles; this limitation is not explicitly taught by Al-bukhari.

Srivastava teaches varying the stringency of the elution medium in recovering phage (paragraph bridging columns 39 and 40).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Al-bukhari and Srivastava are directed to the enrichment of certain selected phage displaying peptides with high affinity against a given target from a library of phage. One of ordinary skill in the art would have recognized the advantages of varying the stringency/elution conditions of Srivastava with the elution step of Al-bukhari for the benefit of producing a library with display members having the highest affinity. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claim 1-7, 9-15, 18, 20-24 and 26-28, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Al-bukhari *et al.*, *Journal of Immunological Methods 264*:163-171 (**2002**), in view of Wittrup *et al.*, U.S. Patent No. 6,423,538 B1.

The limitations of claims 1-7, 9-15, 20-24 and 26-28, and the corresponding disclosure of Al-bukhari is cited above and herein incorporated by reference.

Claim 18 is directed to the use of a mutator strain; this limitation is not explicitly taught by Al-bukhari.

Wittrup teaches the use of mutator strains with phage as a means of producing randomized displayed peptides:

> "An E. coli mutator strain has been used to mutagenize an scFv for affinity maturation by phage display (Low et al., 1996). This approach was successful in identifying a mutant of scFv-4-4-20 with higher affinity for fluorescein using yeast display. A strength of this mutagenesis approach is its simplicity, requiring only E. coli transformation and cell growth. Furthermore the E. coli mutator strain introduces mutations throughout the expression plasmid, and therefore does not bias changes to portions of the scFv believed to be important for determining binding characteristics."

Wittrup, first paragraph in Example 30, in col. 31.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Al-bukhari and Wittrup are directed to the enrichment of certain selected phage displaying peptides with high affinity against a given target from a library of phage, without *a priori* knowledge of a suitable binder. One of ordinary skill in the art would have recognized the advantages of using a mutator strain as taught by Wittrup with

the method of Al-bukhari because of the simplicity of its use in mutating scFv displayed on phage. Therefore, one of ordinary skill in the art would have found the invention to be *prima facie* obvious at the time it was made.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

11/13/06
MY-CHAU T. TRAN
PATENT EXAMINER